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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/928,227	08/09/2001	Michael J. Mahan	220002060725	7979

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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/928,227	MAHAN ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/27/2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-46 are pending.

Claims 1, 8-10, 17, 20-21,24-28, 32, 34, 36-38, 40, and 45 have been amended.

Objections/Rejections Withdrawn

Drawings

1. The drawings are objected to because for not referring to specific embodiment shown has been obviated through amendment of the Brief Description of the Drawings.

Specification

2. The disclosure objected to because of the following informalities has been obviated through amendment of the Specification to remove unclear images.

Claim Rejections - 35 USC § 112

3. Claims 1, 8-9,11-18,20-21,24-25,28,32,36-40, and 45 (paragraph 9, page 7, claim 1; paragraph 11, 13; page 9, second-fourth paragraphs; page 10, paragraphs 1-5; page 11, paragraphs 2-4) rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, have been obviated through amendment of the claims to provide antecedent basis for terms recited and clarification of what is being claimed.

Objections/Rejections Maintained

4. Claims 24-33 and 34-36 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, is maintained for reasons of record in paper number 14, paragraph 7 and responses to arguments set forth below.

5. Claims 24-33 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of stimulating an immune response against a pathogen, does not reasonably provide enablement for stimulation of a protective immune response that can prevent or treat infection caused by the pathogen when dam gene activity is altered. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, is maintained for reasons of record in paper number 14, paragraph 8.

Claim Rejections - 35 USC § 112

6. Claims 1-18, 20-23 (page 7, paragraph 9, claims 1-7; paragraphs 10, 12) rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, are maintained for reasons of record in paper number 14, and responses to arguments set forth below.

Claim Rejections - 35 USC § 102

7. Claims 1-4,6,8-9,11-18,20-21,23-27,29-46 rejected under 35 U.S.C. 102(e) as being anticipated by Vermeulen et al (US Pat. 5,872,104, filing date December 27, 1994) is maintained for reasons of record in paper number 14, paragraph 15, pages 12-14, and responses to arguments set forth below.

8. Claims 1 5,7,10,19 and 22 rejected under 35 U.S.C. 102(b) as being anticipated by Blyn et al is maintained for reasons of record in paper number 14, paragraph 16, pages 14-15, and responses to arguments set forth below.

Response to Arguments

9. Applicant's arguments filed February 27, 2004 have been fully considered but they are not persuasive.

10. The rejection of claims 24-33 and 34-36 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, is traversed on the grounds that:

a. At paragraph 202, (p.54), the specification describes functions and structures that characterize the "agents" in the claims to be an "anti-sense RNA, polypeptide and chelator"; and

b. Asserts that "determining structures of e.g. anti-sense RNA is well known in the art, and thus the term "agent " is enabled by the Specification.

11. It is the position of the examiner that the polynucleotide sequence of the anti-sense RNA that "binds to the upstream control region" of the instantly recited genus of pathogenic bacteria has not been disclosed or described. Paragraph 202 suggests various agents and reagents, but no

specific polynucleotide anti-sense molecules that will block expression of a gene regulated by DAM, that will selective degrade the RNA of the bacteria and not the RNA of the host animal, to selective chelate the DNA or RNA of the pathogenic bacteria and not the infected individual have not been disclosed, nor described at page 54, paragraph 202. The polypeptide has an asserted function, but no specific amino acid structure. No amino acid sequences, or specific polypeptides of a known structure correlated with the asserted biological function, and no anti-sense polynucleotides are disclosed by a nucleic acid sequence that will bind the upstream control regions of in any location, in any specific pathogenic bacterial, which is bacterial specific and will not bind to the infected individuals enzymes, or RNA or DNA.

12. The instant specification fails to comply with the written description requirement, which provides a basis for enablement, wherein the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and no specific agents of any specific structure correlated with function have been so described that the genus of methods and agents have been enabled.

13. As previously pointed out by the examiner at pages 3-4, of paper number 14, a screening assay for identifying a proposed agent with a specific biological activity does not describe what the agent is, wherein the assay would serve to identify the agent at some future date, so the agent could then in turn serve to treat infection caused by a pathogenic bacterial in a method of treating a pathogenic bacterial infection. Agents not described, are not enabled, and the person of skill in the art could not make and use the agents in the instantly claimed methods, nor formulate the agents into the claimed compositions.

14. The rejection of claims 24-33 under 35 U.S.C. 112, first paragraph (scope), because the specification, while being enabling for a method of stimulating an immune response against a pathogen, does not reasonably provide enablement for stimulation of a protective immune response that can prevent or treat infection caused by the pathogen when dam gene activity is altered. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, is traversed on the grounds that:

c. the Specification clearly illustrates that immunization with Dam- bacteria hinders the growth of virulent bacteria in systemic tissues.

15. It is the position of the examiner that none of the claims require the immunization of an individual with Dam- bacteria . What is administered is a "composition" that contains "a pharmaceutically acceptable carrier", which could be saline, and "an active agent", the active agent being any agent with the recited functional characteristics, and not defined by any specific chemical or molecular structure (Instant claim 24).

16. Instant claims 25-33 further limit independent claim 24 through requiring specific phenotypic characteristics to be induced or introduced into the pathogenic bacteria that are causing infection, but the agent that is administered to the subject that is infected, and the degree to which the agent is able to alter DAM activity, albeit a reduction or increase, is not so claimed as to result in a DAM- bacterial infection after that administration of the agent to the subject. Applicant's arguments are not commensurate in scope with the instantly claimed invention.

17. Applicant further traverses the scope of enablement rejection through asserting the claimed invention is directed to "administering a bacteria with a mutation that alters DNA adenine methylase activity and reduces a symptom (Remarks, page 13, paragraph 2)" and asserts that Figure 1, which shows data for S.typhimurium Dam- mutants describe the possibility of testing for Dam-negativity prior to immunization.

18. It is the position of the examiner, upon reconsideration of the claimed invention, of claims 24-33, the claims do not recite the step of "administering a bacteria with a mutation that alters DNA adenine methylase activity and reduces a symptom," nor do the claims recite S.typhimurium, but recite the step of administering a pharmaceutically acceptable carrier and an agent to an infected subject. The agent is not so claimed to be a mutagen that is specific for only the bacterial pathogen's Dam methyltransferase nor is the agent a S.typhimurium Dam- mutant strain; the agent must only phenotypically **alter** the native level of the bacterial pathogen's Dam methyltransferase activity, the pathogen already infecting the subject in vivo.

The degree of alteration of activity of Dam, is not so claimed to require the complete elimination of activity, or overproduction to the point of attenuation of the bacterial pathogen; neither condition is specifically claimed. Again, Applicant's traversal is not commensurate in scope with what is now claimed.

19. Applicant asserts that Ellis and Boslego do not address the present infection, and points to the specification that discloses immunization with Dam- strains of bacteria to generate a protective immune response.

20. It is the position of the examiner that the agent, of the claims, as defined at page 54, paragraph 202, of the instant Specification could be an isolated polypeptide. A polypeptide is a single proteinaceous molecule, a type of protein as discussed by both Ellis and Boslego. The instantly claimed methods do not require the administered agent to be Dam- strains of bacteria, but as previously argued by Applicant, the agent can be a polypeptide. Boslego and Ellis were cited to show how even well known, highly immunogenic polypeptides can induce an immune response, but do not predictably induce a protective immune response. Applicant's arguments are not commensurate in scope with the instantly claimed invention.

21. Applicant in response to the Examiner's request for the identity of genes "in all of the pathogen chromosomes that will alter methylase activity" and result in an alteration in Dam activity and induce protective immunity, directs the examiner's attention to the administration of bacterium that have altered DNA adenine methylase activity, and states that "the specification enables the claimed invention."

22. It is the position of the examiner that the rejection made of record in paragraph 8, was a scope of enablement rejection, with respect to induction of a protective immune response through the administration of any agent that must function as a vaccine. The agent(s) administered must effect any gene, or genes that would alter Dam activity, the alteration not being limited to being an alteration of the coding sequence for Dam activity in a pathogenic bacteria, the bacteria being a wild type bacteria that has already infected a subject , and the bacterium must be altered by the agent in vivo to evidence altered Dam activity upon administration of the agent . No specific genes have been defined, disclosed or described to be

critical sites outside the coding sequence of Dam activity, that are effected by any agent, which results in induction or production of a protective immune response for any and all pathogens. (i.e.) Instant claim 25 requires reduced levels of Dam gene expression in any pathogen, caused by the agent reducing Dam activity in anyway, and is not limited to site directed mutations of Dam methylase of S.typhimurium. Instant claim 28 requires an increase Dam activity, which could be an agent works by increasing the protein's activity, or increases genetic activity; what gene or genes the agent acts upon to increase the activity is not specifically claimed.

The scope of enablement rejection is maintained for reasons of record.

23. The rejection of claims 1-18, 20-23 (page 7, paragraph 9, claims 1-7; paragraphs 10, 12) under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is traversed on the grounds that:

d. The Specification demonstrates over producers and Dam- strains are avirulent;

e. The additional step deemed necessary, "determining the native level of DNA methyltransferase activity" , would result in an unnecessary limitation to the claim;

f. Refers to paragraph [0080] on pages 20-21 as defining both increases or decreases to result in substantially less virulent strains of bacterial relative to wild-type cells.

24. It is the position of the examiner that the claims 1-7 do not require the resultant alterations to produce strains that overproduce Dam activity, nor to be Dam- strains of bacteria; any alteration no matter how big or small a change is claimed. While the specification can be

used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed. Applicant's arguments are not commensurate in scope with what is now claimed.

With respect to the request for an additional essential step in claims 1-18, it is the position of the examiner that the only way to determine an alteration in Dam activity, is to determine the native level of Dam activity as a point of comparison. No point of reference is set forth in the claims; how an alteration can be determined to have been caused by the administered agent is not clearly nor distinctly claimed. No determinations for virulence are required by the claims. The method for reducing bacterial virulence is incomplete, because the level of Dam before and after the contacting step has not been determined, so an alteration need not have been effected by the agent in the contacting step. The structure of the recited agent is not specific for reduction of Dam activity or increasing Dam activity to the point of overproduction and reduction of virulence. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed.

25. In response to the recitation to a relative increase or decrease in Dam activity, Applicant asserts that either change would result in reduce virulence. Upon consideration of Applicant's assertion, the examiner found US Pat. 6,632,430 to teach with increase activity of Dam, increase

production of virulence factors would result (see col. 2, lines 43-62). Through increase methylation, which is not overproduction, would induce production of virulence factors which results in a more highly virulent, pathogenic bacteria, rather than attenuation due to over production of Dam methylase, or production of undesired methylation reactions. The general increase of Dam activity, that is not over production, would or could result in a more pathogenic bacteria. The invention is not distinctly claimed despite the teaching of paragraph [0080], the art teaches that with an increase of Dam activity, induction of virulence factors results. The claims are not limited to administration of avirulent Dam mutant strains of bacteria as the agent, the mutant bacteria being one in which the gene for Dam is known in the art or is disclosed herein.

While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed.

26.

Claim Rejections - 35 USC § 102

27. The rejection of claims 1-4,6,8-9,11-18,20-21,23-27,29-46 under 35 U.S.C. 102(e) as being anticipated by Vermeulen et al (US Pat. 5,872,104, filing date December 27, 1994), set forth in pages 12-14, of paper number 14, is traversed on the grounds that:

28. Vermeulen discloses "increasing the effectiveness of MLS antibiotics (col. 5, lines 10-24) based on the contemplation that "methylation.... Plays a role in all mechanisms of resistance of a microorganism to an antimicrobial agent", asserts that Vermeulen does not teach or suggest methods for reducing the virulence or pathogenicty of a pathogenic bacteria , and states that

Vermeulen administers an antibiotic in combination of a general methylase inhibitor which is not a specific DNA adenine methylase inhibitor, and cites the instant Specification [00210], page 57. which teaches **sinefungin** to block all DNA methylases including mammalian cytosine methylase, and thus would not be useful as a chemotherapeutic agent against bacteria.

29. It is the position of the examiner that the agent of claims 1-4, 6,8-9,11-18,20-21 and 23, and composition claims 34-36, need not come in contact a human or mammalian methyltransferase, only bacteria, therefore utilization of the sinefungin DNA methylase blocker would not come in contact with mammalian cytosine and would serve to reduce DNA methyltransferase activity and could be used in the formulation of a composition with the recited biological activity.

30. All of the claims recite "open" language, thus not excluding the presence of an additional agent, such as an antibiotic together with a methylase inhibitor, to reduce the native level of methylase substrate, thus indirectly reducing DNA methyltransferase activity, as well as inhibition of SAM and SAH enzymes will lower the methylation of adenine (see col. 22, lines 1-20).

31. Additionally, Vermeulen et al disclose agents other than sinefungin (see office action, paper number 14, pages 12-14, paragraph 15, which is incorporated by reference herein,) for inhibiting bacterial methyltransferases, to include DNA methyltransferases, either directly or indirectly) which would serve to alter DNA methyltransferase activity. At col. 2, line 9, DNA methylase inhibition is disclosed.

32. With respect to administration of an agent composition to a subject, Vermeulen et al disclose a number agents that will alter Dam activity, but need not directly act upon the DNA

methylase protein or coding region, or upstream DNA control region, and would function to alter the bacteria's native level of DNA methylase activity (see paragraph 15, of paper number 14, pages 12-14). In view of the claim reciting the broad genus of "agent", the inhibitors of Vermeulen et al, used in the a method of treating bacterial infection, would be a method of reducing bacterial virulence, and reducing pathogenicity, because the bacteria would die, upon treatment with a methylase inhibitor and an antibiotic, and/or no longer proliferate.

33. Applicant traverses the Vermeulen reference as not teaching DNA adenine methylase (DAM) inhibitors as specified in independent claims 1 and 19.

34. It is the position of the examiner that claims 1 and 19 only require a change in phenotype, an alteration of "DNA methyltransferase activity", which is not required to be a specific genetic change in the coding sequence for bacterial DNA methyltransferase , nor does the claim require a specific inhibitor of a bacterial DNA methyltransferase in the enzyme's active site; only a change in activity, based upon any type of cellular change is required to be induced by the agent administered. Applicant's arguments are not commensurate in scope with the instantly claimed invention. The claims remain rejected for reasons of record in paper number 14 and responses to remarks set forth above.

35. The rejection of claims 1 5,7,10,19 and 22 under 35 U.S.C. 102(b) as being anticipated by Blyn et al is traversed on the grounds that:

g. "any resulting effect on virulence or pathogenictiy is not discussed.";

h. Blyn doe not teach or suggest contacting or administering to the bacteria an agent that alters the bacteria's native level of DNA methyltransferase activity thereby altering the bacteria's native level of methylation.; and

i. Concludes that "merely "contacting " bacteria with a plasmid does not transform the bacteria and additional procedures are necessary for transformation."

36. It is the position of the examiner that:

j. the bacterial strains of Blyn et al were contacted with an agent that altered the bacteria's native level of DNA methyltransferase activity (see page 4045, col. 1, bottom half of abstract) "Dam methylase levels affected the regulation of pap transcription; papa transcription was absent in dam-E.coli. Moreover, transition from the phase off to phase on state was not observed in E.coli expressing aberrantly high levels of Dam."

k. The expression or non-expression of pap pilin, a known virulence factor of E.coli (see page 4045, col. 1, Introduction section) is discussed to be regulated by Dam methylase levels.

1. The transformed E.coli expressed aberrantly high levels of Dam (see abstract, page 4045; page 4049, col. 2, paragraphs 2-5), specifically 3.5 to 4.6 times the control cell levels which is also an increase level over the native wild-type cells (see page 4049, col. 2, paragraphs 4-5) which resulted in an altered level of Dam methyltransferase in the bacterial cell. The reference inherently anticipates the instantly claimed invention Atlas

Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states "Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. "The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art".

Conclusion

37. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

38. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on 7:30-5:00 M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
May 25, 2004

L. F. Smith

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